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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/677,374	09/15/2000	Michael A. Kuzyk	1115-005/ddh	2747

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	20

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/677,374	KUZYK ET AL.	
	Examin r	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communicati n appears on the cover sheet with th c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,42,43 and 50-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42,43 and 50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed August 18, 2003.

2. The amendment submitted August 18, 2003 is acknowledged. Claims 1-39, 41 and 44-49 have been cancelled. Claims 50-55 have been added.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

4. In view of Applicant's amendment and Response, the following Objections and rejections have been withdrawn:

a) Objection to the specification, page 2, paragraph 2 of the previous Office action.

b) Objection to the specification, page 2, paragraph 3 of the previous Office action.

c) Objection to claim 43, page 2, paragraph 4 of the previous Office action.

d) Objection to claim 47, page 3, paragraph 3 of the previous Office action.

e) Objection to the Drawings, page 3, paragraph 6 of the previous Office action.

f) Rejections of claims 40-49, page 9-10, paragraph 9 of the previous Office action.

5. The rejection of claims 40, 42-43 and newly submitted claims 50-55 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 3-5, paragraph 7 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a written description rejection.*

The specification broadly describes as a part of the invention polypeptides having SEQ ID No: 2 (elected sequence). The specification teaches that any molecule in which the amino acid sequence has undergone glycosylation, phosphorylation, and/or lipidation pattern or any other process which has modified the amino acid sequence is intended to be defined as a mutant. The specification teaches that "some variants falling within this invention possess amino acid substitutions, deletions, and/or insertions provided that the final construct possesses the desired ability of OspA (page 10).

Applicant has broadly described the invention as embracing any substitution, insertion or deletion change of amino acid throughout the length of the polypeptides sequence. Variants, homologs, degenerates, derivatives or fragments of SEQ ID NO: 2 correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 U.S.C. 112, first, paragraph. The specification provides insufficient written description to support the genus encompassed by the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID No: 2 (elected sequence) the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID No: 2 (elected sequence) and not the full breadth of the claim (i.e. variants, homologs, degenerates, derivatives or fragments of SEQ ID No: 2) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed is not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant urges that the specification has been amended or more clearly define the variants that are encompassed in the instant claims. Applicant submits that there was at the time of filing methodology to permit screening of variants having substitutions, deletions and/or insertions and further it would not take undue experimentation to generate the variants and then screen the variants.

Applicant's arguments filed August 18, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to that the specification is enabled for the full scope of the claims and therefore does not meet the written description requirement as set forth in 35 U.S.C. 112, first paragraph. The specification broadly describes a genus of proteins. Applicant has provided no structural description accompanying the variant language (i.e. sequence having similarity to SEQ ID NO:1, 3 and 5 that do not alter one of the immunogeneicity and function of said protein) recited in the claims. The specification defines the term "variant" as any molecule in which the amino acid sequence, glycosylation, phosphorylation and/or lipidation pattern or any other feature of a naturally occurring molecule which has been modified covalently or non-covalently and is intended to include mutants. The specification teaches that some of the variants falling within the invention possess amino acid substitutions, deletions and/or insertions provided that the final construct possesses the desired ability of OspA. (page 10). The requirement under 35 U.S.C. 112, first paragraph written description requires that Applicant's were in possession of the claimed polypeptides at the time of filing. Applicant were in possession of the amino acid sequences as set forth in SEQ ID NOs:1-6 . However, there is no requirement

under 35 U.S.C. 112, first paragraph that requires "one of skill in the art to find amino acid sequence that are variants of SEQ ID Nos:1-6 that do not alter one of the immunogenicity and function of said protein". What are the specific locations in which substitutions, insertions or deletions can be made to obtain a protein that possess the same or similar characteristics to SEQ ID Nos:2, 4 or 6? What modification can be made to the nucleic acid sequences as set forth in SEQ ID Nos:1, 3 or 5 to arrive at the claimed protein? The specification has not shown any specific examples of the claimed variants of SEQ ID Nos: 2,4 or 6, nor has the specification taught any proteins that are encoded by sequences that have similarity to SEQ ID NOS:1, 3 or 5 and do not alter one of the immunogenicity and function of said protein. While the use of mutagenesis techniques are known in the art, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. Therefore, only proteins as set forth in SEQ ID Nos.2, 4, or 6 and not the full breadth of the claim (i.e. variants of SEQ ID NO:2, 4 or 6 meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Applicant's substitute specification filed August 18, 2003 has not been entered because it does not conform to 37 CFR 1.125(b) because: a marked up copy of the changes has not been provided.

6. The rejection of claims 40, 42-43 and newly submitted claims 50-55 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 5-8, paragraph 8 of the previous Office Action.

The rejection was on the grounds that Claims 40-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID No: 2 (elected sequence), does not reasonably provide enablement for variants, homologs, degenerates, derivatives or fragments of SEQ ID No: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is enabling only for the polypeptides of SEQ ID No: 2 and not protein fragments or variants of SEQ ID No: 2 as disclosed in the specification. The specification teaches that any molecule in which the amino acid sequence has undergone glycosylation, phosphorylation, and/or lipidation pattern or any other process which has modified the amino acid sequence is intended to be defined as a mutant. The specification teaches that "some variants falling within this invention possess amino acid substitutions, deletions, and/or insertions provided that the final construct possesses the desired ability of OspA (page 10).

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant

disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

The claims of the instant application are not only drawn to a purified amino acid molecule but are also drawn to fragments of the claimed protein. There is no guidance provided in the specification as how one would begin to choose "protein fragments" The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other proteins having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use proteins that are variants or fragments of SEQ ID No: 2 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the amino acid's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Applicant urges that the specification has been amended or more clearly define the variants that are encompassed in the instant claims. Applicant submits that there was at the time of filing methodology to permit screening of variants having substitutions, deletions and/or insertions and further it would not take undue experimentation to generate the variants and then screen the variants.

Applicant's arguments filed August 18, 2003 have been fully considered but they are not persuasive. The specification does not provide enablement for the full scope of the claimed invention. Applicant has provided no structural description accompanying the variant language recited in the claims. While recombinant, mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable. One skilled in the art would not expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptide is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides. The specification has not shown any specific examples of the claimed variants of SEQ ID NO:2, 4 or 6 that do not alter one of the immunogenicity and function of said protein. It must be remembered that there is no requirement under 35 U.S.C. 112, first paragraph that requires "one of skill in the art to

find polypeptides that are variants of SEQ ID NO:2, 4 and 6 that do not alter one of the immunogenicity and function of said protein". Therefore a structural description is required. One skilled in the art would require guidance in order to make and use the claimed invention in scope with the claims.

7. The rejection of claims 40, 42-43 and newly submitted claims 50-55 under 35 U.S.C. 102(b) is maintained for the reasons set forth on pages 10-11, paragraph 10 of the previous Office Action.

The rejection was on the grounds that Anderson et al teach 17-kilodalton antigens from *Rickettsia rickettsii, R. conorii, R. prowazekii and R. typhi.* It would be inherent in the teachings of the prior art that the 17-kilodalton antigens would be cross-reactive with the anti-*P. salmonis* serum since Anderson et al teach that the 17-kDa antigen is commonly conserved among members of the genus *Rickettsiae* (page 5201, 1st column).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Anderson et al teach a 17kD protein that is conserved within the four *Rickettsia* species studied. Applicant urges that the protein of the instant invention is not 17kD but rather is approximately 16kD as determined by SDS PAGE Applicant urges that the instantly claimed protein ranges in length from about 15.5 to 17.7 kDa. Applicant urges that the protein of the prior art has only 41% and 62% similarity to the claimed amino acid sequences. Applicant urges that Anderson et al

teaches away from the claimed invention because Anderson et al teach that the gene is commonly conserved and not the protein.

Applicant's arguments filed August 18, 2003 have been fully considered but they are not persuasive. The claims are drawn to a protein of 17kDa as determined by SDS PAGE encoded by one of SEQ ID Nos: 1,3, 5 and sequences having similarity to SEQ ID Nos. 1,3 and 5 that do not alter one of the immunogenicity and function of said protein. Anderson et al teach 17-kilodalton antigens from *Rickettsia rickettsii, R. conorii, R. prowazekii and R. typhi.* Anderson et al teach the gene encoding the 17-kDa antigen from *Rickettsia rickettsii* and transcription and post-translation modification. It would be inherent in the teachings of the prior art that the 17-kilodalton antigens would be cross-reactive with the anti-*P. salmonis* serum since Anderson et al teach that the 17-kDa antigen is commonly conserved among members of the genus *Rickettsiae.* Applicant admits in this response that the proteins of the prior art have 41% and 62% similarity to the claimed amino acid sequences which meets the claim limitations of "sequences having similarity to SEQ ID Nos. 1, 3 and 5 that do not alter one of the immunogenicity and function of said protein". Applicant has provided no side-by-side comparison to show that the protein of the prior art is not the same as the proteins of the claimed invention. Therefore, Anderson et al anticipates the claimed invention.

New Grounds of Rej ction Nec ssitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 40 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim is indefinite because the claims recite "sequences having similarity to SEQ ID Nos. 1,3 and 5 that do not alter one of the immunogenicity and function of said protein". It is unclear as to what the Applicant is referring?

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
November 16, 2003

MARK NAVARRO
PRIMARY EXAMINER